Progesterone Supplementation and the Prevention of Preterm Birth

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Preterm birth is currently the most important problem in maternal-child health in the United States and possibly throughout the world. It complicates one in eight US deliveries, and accounts for over 85% of all perinatal morbidity and mortality. Although survival of preterm infants has increased steadily over the past four decades—due in large part to the use of antenatal corticosteroids, improvements in neonatal resuscitation, and the introduction of neonatal intensive care units—efforts to prevent preterm birth have been largely unsuccessful. On February 3, 2011, the US Food and Drug Administration (FDA) approved the use of progesterone supplementation (hydroxyprogesterone caproate) during pregnancy to reduce the risk of recurrent preterm birth in women with a history of at least one prior spontaneous preterm delivery. This is the first time that the FDA has approved a medication for the prevention *of preterm birth, and represents the first approval of a drug specifically for use in pregnancy in almost 15 years. This article reviews the evidence behind the use of progesterone for the prevention of preterm birth, and provides guidelines for the use of progesterone supplementation in clinical practice. A number of areas of ongoing controversy are addressed, including the optimal formulation and route of administration, the safety of progesterone supplementation in pregnancy, and its proposed mode of action.*
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Preterm (premature) birth refers to any delivery occurring prior to 37-0/7 weeks (259 days) of gestation. In developed countries, preterm birth complicates one in eight births, and accounts for more than 85% of all perinatal morbidity and mortality. Although the ability of obstetric care providers to identify women at high risk for preterm birth has improved (due in large part to

the introduction of transvaginal cervical length measurements and cervicovaginal fetal fibronectin testing), efforts to prevent preterm birth have been largely unsuccessful. On February 3, 2011, the US Food and Drug Administration (FDA) approved the use of progesterone supplementation—specifically, hydroxyprogesterone caproate injections (Makena™; KV Pharmaceutical Co., St Louis, MO)—to reduce the risk of recurrent preterm birth in women with a singleton pregnancy who have a history of at least one prior spontaneous preterm delivery.[1] This is the first time that the FDA has approved a medication for the *prevention* of preterm birth, and represents the first approval of a drug specifically for use in pregnancy in almost 15 years.

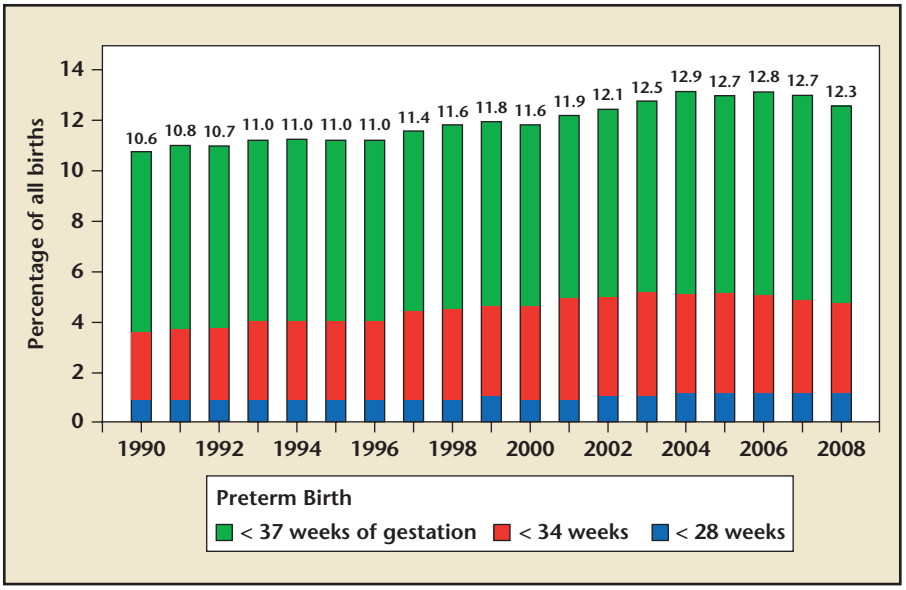

Figure 1. *Incidence of preterm birth in the United States, 1990-2008. The incidence of preterm birth in the United States is shown, including overall preterm birth (< 37 weeks of gestation), < 34 weeks of gestation, and < 28 weeks of gestation. Data are from the CDC/National Center for Health Statistics (http://www.cdc.gov/nchs/; accessed February 18, 2011).*

Scope of the Problem

In 2008, the latest year for which data are currently available, the overall preterm birth rate in the United States was 12.3%.[2] This represents a 35% increase in overall preterm births over the past 25 years, and has been accompanied by an increase in moderately preterm (28-34 weeks) and extreme preterm births (< 28 weeks). It is only in the last two to three years that there has been a decrease in the preterm birth rate from 12.8% in 2006 to 12.7% in 2007 and 12.3% in 2008 (Figure 1). The reasons for this recent decrease are not immediately clear. It may represent a plateauing of the risk factors for preterm birth (including advanced maternal age and the use of assisted reproductive technology), a systematic change in the management of pregnancies that leads to late preterm births (defined as delivery from 34-37 weeks, which accounts for 75% of all preterm births), the use of progesterone supplementation (discussed below),[3] or a combination of these factors.

Causes of Preterm Birth

The timely onset of labor and birth is a critical determinant of perinatal outcome. Preterm birth represents a syndrome rather than a diagnosis because the etiologies are varied. Approximately 20% of preterm deliveries are iatrogenic and are performed for maternal or fetal indications, including, among others, preeclampsia, placenta previa, prior high-vertical ("classical") cesarean delivery, monochorionic-monoamniotic twins, cholestasis, intrauterine growth restriction, and nonreassuring fetal testing. Of the remaining cases, approximately 20% to 30% occur in the setting of preterm premature rupture of the membranes (PPROM), 20% to 25% result from intra-amniotic infection and/or inflammation, and the remaining 25% to 30% are due to spontaneous (unexplained) preterm labor[4,5] (Figure 2).

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Identification of Women at Risk of Preterm Birth

The ability of obstetric care providers to identify women at risk for preterm birth has improved significantly over the past few years. This is due to the introduction of a number of predictive tests, including:

- **Risk Factor Scoring.** A number of risk factors for preterm birth have been identified (Table 1). Several scoring systems have been developed based on these historic/epidemiologic risk factors and daily habits in an attempt to predict women at risk for preterm birth. Unfortunately, reliance on risk factor–based screening protocols alone will fail to identify over 50% of pregnancies that deliver preterm (low sensitivity) and the majority of women who screen positive will ultimately deliver at term (low positive predictive value).[6,7] The single

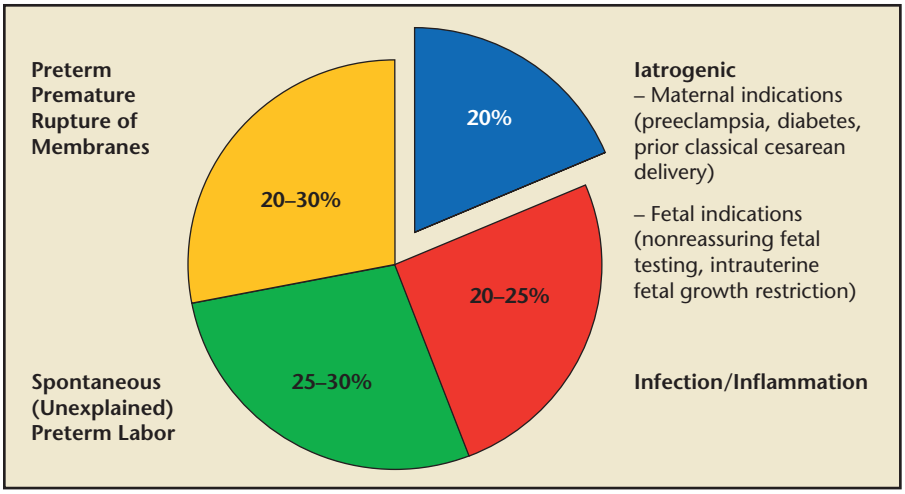

Figure 2. *Major causes of preterm birth.*

Table 1
Risk Factors for Spontaneous Preterm Birth

Nonmodifiable Risk Factors	
Prior preterm birth	Cervical injury or anomaly
African-American race	Uterine anomaly
Age < 18 years or > 40 years	Excessive uterine activity (?)
Poor nutrition	Premature cervical dilatation (> 2 cm) or effacement (> 80%)
Low prepregnancy weight	
Low socioeconomic status	Overdistended uterus (twins, polyhydramnios)
Absent prenatal care	Vaginal bleeding
Potentially Modifiable Risk Factors	
Cigarette smoking	Lower genital tract infections (including bacterial vaginosis, *Neisseria gonorrhoea, Chlamydia trachomatis*, Group B *Streptococcus*, *Ureaplasma urealyticum*, and *Trichomonas vaginalis)*
Illicit drug use	
Anemia	
Bacteriuria/urinary tract infection	
Gingival disease	High personal stress (?)
Strenuous work/work environment (?)	

greatest risk factor for preterm birth is a history of a prior unexplained spontaneous preterm delivery.

- **Sonographic Cervical Length Measurement.** A strong inverse correlation exists between residual cervical length as measured by transvaginal ultrasound and preterm birth.[8,9] If the cervical length is < 10th percentile for gestational age in the midsecond trimester, the pregnancy is at a sixfold increased risk of delivery prior to 35 weeks.[8] A cervical length of < 15 mm at 22 to 24 weeks occurs in < 2% of low-risk women, but is predictive of delivery prior to 28 weeks and 32 weeks in 90% and 60% of cases, respectively.[9]
- **Biochemical Tests.** A number of biochemical and endocrine markers (including estriol, corticotrophin-releasing hormone, and activin A) are under investigation to determine whether they can be used to identify women at risk for preterm birth. The only test that is currently FDA approved and recommended by The American College of Obstetricians and Gynecologists (ACOG) for this indication is the measurement of fetal fibronectin (fFN) in cervicovaginal secretions.[10-12] Elevated levels of cervicovaginal fFN (defined as > 50 ng/mL) at 22-0/7 through 34-6/7 weeks of gestation are associated with an increased risk of preterm birth.[10] However, in a low-risk population, the positive predictive value of a positive fFN test at 22 to 24 weeks of gestation for spontaneous preterm delivery prior to 28 weeks and 37 weeks of gestation is only 13% and 36%, respectively.[11] The primary value of this test lies in its negative predictive value (99% of patients with a negative fFN test will not deliver within 7 days[12]), which may prevent unnecessary hospitalization and medical intervention.

Prevention of Preterm Birth

There are no consistent data that any intervention (including hydration, antibiotics, or tocolytic therapy) can delay delivery in women for longer than 24 to 48 hours once they have presented in preterm labor. For this reason, much attention has focused on preventative strategies. Although several strategies have been proposed (Table 2),[13-18] the prevention of preterm birth has been largely unsuccessful. It is not surprising, therefore, that there has been much excitement about the recent FDA approval of progesterone supplementation for the prevention of preterm birth.

Progesterone Supplementation and the Prevention of Preterm Birth

A detailed discussion of the hormonal, molecular, and genetic factors

Table 2
Strategies for the Prevention of Preterm Birth

Strategies That Have Limited or No Proven Efficacy
Bed rest[13]
Pelvic rest (avoidance of intercourse)
Intensive education and prenatal care
Screening and treatment of asymptomatic lower genital tract infections
Treatment of gingival disease[16]
Empirical broad-spectrum antibiotic therapy
Prophylactic tocolytic therapy
Strategies That May Have Some Benefit
Prevention and early diagnosis of sexually transmitted and genitourinary infections
Treatment of symptomatic lower genital tract infection[15]
Cessation of smoking and illicit substance use
Prevention of multiple pregnancies
Elective (prophylactic) cervical cerclage, if indicated
Folic acid supplementation[18]

associated with preterm parturition is beyond the scope of this article, and has been reviewed in detail elsewhere.[19-21] Accumulating evidence suggests that the myometrial activity associated with preterm labor results primarily from a release of the inhibitory effects of pregnancy on the myometrium rather than an active process mediated through the release of uterine stimulants, and progesterone appears to play a central role in this regard. In the first trimester, progesterone produced by the corpus luteum is critical to the maintenance of early pregnancy until the placenta takes over this function at 7 to 9 weeks of gestation, hence its name (*pro-gest*ational st*e*roidal ket*one*). Indeed, removal of the source of progesterone (the corpus luteum)[22] or administration of a progesterone receptor antagonist[23] readily induces abortion before 7 weeks (49 days) of gestation. The role of progesterone in later pregnancy, however, is less clear.

Recent data suggest that progesterone may be important in maintaining uterine quiescence in the latter half of pregnancy by limiting the production of stimulatory prostaglandins and inhibiting the expression of contraction-associated protein genes (ion channels, oxytocin and prostaglandin receptors, and gap junctions) within the myometrium.[19-21] It is now clear that, although levels of progesterone in the maternal circulation do not change significantly in the weeks preceding labor, the onset of labor both at term and preterm is associated with a functional withdrawal of progesterone activity at the level of the uterus.[19-21,24-27] It is data such as these that provide the rationale behind the use of progesterone supplementation to prevent preterm labor and birth.

Summary of Clinical Trials

Multiple trials have examined the use of progesterone in various preparations for the prevention of recurrent preterm birth. One of the earliest trials, reported in 1975, randomized 43 high-risk patients to weekly intramuscular 17α-hydroxyprogesterone caproate (17P) or placebo.[28] The authors found a protective effect of progesterone, with a significantly longer mean duration of pregnancy, higher mean birthweight, and lower perinatal mortality rate. A number of subsequent trials yielded conflicting results.[29-31] This prompted Professor Marc Keirse to perform a meta-analysis of seven published trials on the use of progesterone prophylaxis in high-risk populations. Published in 1990,[32] the author's study reported a significant reduction in the rate of preterm labor, preterm birth, and birthweight < 2500 g in those subjects who received progesterone prophylaxis, but it was not clear from these data whether this translated into an overall reduction in perinatal mortality and morbidity. For reasons that remain unclear, the use of progesterone supplementation for the prevention of preterm birth fell out of favor in the 1990s. It was not until 2003, with the publication of two well-designed, high-profile, randomized

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clinical trials[33,34] that the interest in this preventative strategy was reinvigorated. Let us examine the data based on the clinical indication.

(1) **Progesterone Supplementation in Women With a History of a Spontaneous Preterm Birth.** There is increasing evidence that progesterone supplementation can reduce the rate of spontaneous preterm birth in women at high risk by virtue of a prior spontaneous preterm birth:

- **Maternal-Fetal Medicine Units Network Trial:** Meis and coinvestigators[34] randomly assigned 459 patients with a documented history of a prior spontaneous preterm delivery to weekly intramuscular injections of 17P (250 mg) or placebo beginning at 16 to 20 weeks of gestation and continuing until 36 weeks. Women randomized to 17P prophylaxis had a significantly reduced risk of recurrent preterm birth at all gestational ages studied: < 37 weeks (36% vs 55% in the placebo group [relative risk {RR}, 0.66; 95% confidence interval {CI}, 0.54-0.81]), < 35 weeks (21% vs 31% [RR, 0.67; 95% CI, 0.48-0.93]), and < 32 weeks (11% vs 20% [RR, 0.58; 95% CI, 0.37-0.91]). Moreover, infants born to mothers treated with 17P had less perinatal morbidity and significantly reduced rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen. There was no evidence of virilization of female offspring, which was a theoretical concern of this therapy.
- **Brazilian Trial:** da Fonseca and coinvestigators[33] randomly assigned 142 women at high-risk for preterm delivery (based on at least one previous spontaneous preterm birth, prophylactic cervical cerclage, or uterine malformation) to daily supplementation with progesterone vaginal suppositories (100 mg) or placebo from 24 through 34 weeks of gestation. Women randomized to progesterone prophylaxis had a significantly reduced risk of recurrent preterm birth at all gestational ages studied: < 37 weeks (14% vs 29% in the placebo group; $P < .05$), and < 34 weeks (3% vs 19%; $P < .05$). In addition, by monitoring all patients with an external tocodynamometer once a week for 60 minutes, the investigators were also able to demonstrate a significant difference in the frequency of spontaneous uterine contractions between the two groups, suggesting that progesterone supplementation may exert its effect by maintaining uterine quiescence in the latter half of pregnancy.
- **Not All Studies Show a Benefit:** The largest randomized trial of progesterone supplementation for the prevention of recurrent preterm birth did not find a benefit.[35] In this trial, 659 women with a history of a prior spontaneous preterm birth were randomly assigned to self-administer progesterone gel (90 mg) or placebo vaginally each day from between 18 to 23 weeks and 37 weeks of gestation. Rates of recurrent preterm birth in this cohort were high, approximately 25% prior to 35 weeks and 40% prior to 37 weeks of gestation. Progesterone supplementation did not significantly reduce the frequency of preterm birth at any gestational age compared with placebo, and there were no differences among the groups for any maternal or neonatal outcome measure. The reason for the discrepancy between this and other trials is unclear, but may have to do with the type, dose, and route of administration of progesterone[36,37] (discussed below).
- **Results of Meta-Analyses:** Subsequent meta-analyses of these and other randomized trials have concluded that progesterone supplementation is indeed protective against recurrent preterm birth.[38-41] Such studies suggest that the rate of recurrent preterm birth with the use of prophylactic progestational agents is approximately 25% to 31% compared with 33% to 47% in placebo controls. However, statistically significant reductions in the clinical sequelae of preterm birth (perinatal mortality or prematurity-related morbidity) were not consistently demonstrated, likely because of a lack of adequate power to evaluate these rare outcomes.

(2) **Progesterone Supplementation in Women With Cervical Shortening.** Cervical shortening is a known risk factor for preterm birth in both low- and high-risk populations.[8,9,42] In a high-profile, randomized, placebo-controlled trial, 250 asymptomatic women with a short cervix (≤ 15 mm) on transvaginal ultrasound at 20 to 25 weeks of gestation were treated with either vaginal progesterone (200 mg each night) or placebo.[42] Progesterone administration significantly reduced the rate of spontaneous preterm birth before 34 weeks (19.2% vs 34.4% in controls [RR, 0.56; 95% CI, 0.36-0.86]). Since that publication, a small secondary analysis[43] and a larger randomized trial[44] have confirmed this observation. In the largest of these studies,[44] 458 asymptomatic women with a singleton pregnancy and a

sonographic short cervix (10-20 mm) at 19 to 24 weeks of gestation were randomly allocated to receive vaginal progesterone gel (90 mg) or placebo daily from 20 to 24 weeks until 37 weeks of gestation. Women randomized to receive vaginal progesterone had lower rates of preterm birth than those allocated to placebo at all gestational ages studied: < 35 weeks (14.5% vs 23.3% [RR, 0.62; 95% CI, 0.42-0.92]), < 33 weeks (8.9% vs 16.1% [RR, 0.55; 95% CI, 0.33-0.92]), and < 28 weeks (5.1% vs 10.3% [RR, 0.50; 95% CI, 0.25-0.97]). This translated also into a significant reduction in respiratory distress syndrome, very low birth weight infants, and overall neonatal morbidity and mortality. Whether progesterone acts by attenuating further cervical shortening is not yet clear.[45,46]

(3) Progesterone Supplementation in Women With Other Risk Factors for Preterm Birth. There is limited high-quality evidence regarding progesterone supplementation in women with other high-risk conditions.[47] Some of these are discussed below.

- **Positive fFN:** Although a positive cervicovaginal fFN test is a risk factor for preterm birth,[10-12] there is no information on use of progesterone supplementation in such women.
- **PPROM:** Approximately 20% to 30% of preterm deliveries occur in the setting of PPROM. A recent placebo-controlled, randomized trial found no evidence that weekly injection of 17P is able to extend gestation in women presenting with PPROM at 20 to 30 weeks of gestation.[48] However, women with a history of preterm birth due to PPROM were included in the prior randomized clinical trials,[33,34] and may benefit from progesterone supplementation.
- **Women With a Cerclage:** Cervical cerclage is the treatment of choice for women with a history of prior midtrimester pregnancy losses due to cervical insufficiency. It is not clear whether 17P provides additional benefit to women with a cervical cerclage in place. In a secondary analysis of a randomized trial evaluating cerclage, women with a prior spontaneous preterm birth, short cervix (≤ 25 mm), and a cerclage had the same frequency of delivery before 35 weeks of gestation as comparable women who did not receive progesterone supplementation.[49]
- **Acute Preterm Labor:** Studies to date have focused on the use of progesterone to *prevent* preterm birth in women at high risk. What about the use of progesterone to *treat* women in preterm labor? Although no studies have used progesterone in the setting of acute preterm labor, several have investigated the use of progesterone in women who remained undelivered after an episode of preterm labor. In one such study, 60 women who remained undelivered after an episode of preterm labor were randomized to treatment with 17P (341 mg twice weekly) or observation alone. Women who received 17P experienced less shortening of the cervix and a reduced rate of preterm delivery (odds ratio [OR], 0.15; 95% CI, 0.04-0.58).[45] A similar trial randomly assigned 70 women who remained undelivered after an episode of preterm labor to progesterone vaginal suppository (400 mg daily) or no intervention.[50] In this cohort, progesterone maintenance therapy after successful parenteral tocolysis was associated with a significantly longer latency to delivery (36.1 ± 17.9 days vs 24.5 ± 27.2 days), higher birth weight (3101.5 ± 587.9 g vs 2609.4 ± 662.9 g; $P = .002$), and lower incidence of respiratory distress syndrome (10.8% vs 36.4%; $P = .021$). However, there was no difference in the overall rate of preterm birth, admissions for recurrent preterm labor, or admissions to the neonatal intensive care unit.
- **Multiple Gestation:** There is now consistent evidence from several clinical trials that progesterone supplementation does not prolong gestation or improve perinatal outcome in women with multiple gestations. In a study modeled on the Meis trial,[34] 661 healthy women with *twin gestations* were randomized to weekly intramuscular injections of 17P (250 mg) or matching placebo starting at 16 to 20 weeks of gestation and ending at 35 weeks.[51] The composite primary outcome of delivery or fetal death < 35 weeks occurred in 41.5% of pregnancies in the progesterone group and 37.3% of those in the placebo group (RR, 1.1; 95% CI, 0.9-1.3). Few adverse events occurred and the rate did not differ between the two groups. Interestingly, a subsequent secondary analysis of this study reported that 17P failed to prevent early preterm birth even in those twin pregnancies with cervical shortening.[52] In a second randomized trial (Study Of Progesterone for the Prevention of Preterm Birth In Twins

[STOPPIT]),[53] 500 cases of twin pregnancy were randomized to receive daily vaginal progesterone gel (90 mg) or placebo from 24 weeks through 34 weeks of gestation. The combined proportion of intrauterine death or delivery < 34 weeks was similar for both groups: 24.7% (61/247) in the progesterone group and 19.4% (48/247) in the placebo group (OR, 1.36; 95% CI, 0.89-2.09). The rate of adverse events did not differ between the two groups. A meta-analysis including these two trials and a smaller one (26 subjects) confirmed that progesterone supplementation does not prevent preterm birth in twin gestation (pooled OR, 1.16; 95% CI, 0.89-1.51).[53] This was confirmed by another randomized clinical trial published in 2011.[54] Similar data have been reported in *triplet pregnancies*. In a randomized trial of 134 healthy women with triplets, the rate of fetal loss or preterm birth < 35 weeks was not significantly different between women assigned to receive 17P (250 mg intramuscularly once per week) and those who received a placebo from 16 to 21 weeks through 35 weeks of gestation.[55] Another placebo-controlled, randomized trial of prophylactic 17P supplementation in 81 cases of triplet pregnancy also found no benefit, as well as a possible increase in midtrimester pregnancy loss.[56]

The observation that progesterone supplementation does not prevent preterm birth in multiple pregnancy suggests that the mechanism leading to preterm labor and delivery in multiples—namely excessive uterine stretch—is different from that in singletons (see discussion above). This argument is supported by a recent study showing that progesterone does not inhibit stretch-induced MAPK activation or gene expression in myometrial cells in vitro.[57]

Recommendations for the Use of Progesterone Supplementation in Clinical Practice

Given supportive statements by the ACOG,[58] the recent FDA approval handed down on February 3, 2011,[1] and the absence of proven alternatives, *the use of progesterone supplementation to reduce the risk of recurrent preterm birth in women at high risk can no longer be regarded as investigational*. Recommendations for the use of progesterone supplementation to prevent preterm birth are summarized in Table 3. Although secondary analyses of clinical trials have suggested that women who benefit most from 17P supplementation are those who experienced a prior spontaneous preterm birth < 34 weeks,[59] it is reasonable to offer such prophylaxis to all women with a prior spontaneous preterm delivery. If used, progesterone supplementation should generally be initiated between 16 and

Table 3
Recommendations for Progesterone Supplementation to Prevent Preterm Birth

Indication	Progesterone Supplementation Indicated?	Formulation, Dose, and Route of Administration	FDA Approved?	Reference
Prior spontaneous preterm birth	Yes	17α-hydroxyprogesterone caproate 250 mg intramuscularly weekly from 16-20 weeks through 36 weeks of gestation	Yes	34
Cervical shortening (≤ 15 mm prior to 24 weeks)	Yes	Progesterone suppository 90-200 mg vaginally each night from time of diagnosis through 36 weeks of gestation	No	42, 44
Multiple pregnancy (twins or triplets)	No	—	No	51-56
Preterm premature rupture of membranes	No	—	No	48
Positive fetal fibronectin (fFN) test	No	—	No	—
Cervical cerclage in place	No	—	No	49
Undelivered after an episode of preterm labor	Unclear	—	No	45, 50

20 weeks of gestation, although patients were enrolled in trials up to 26.9 weeks,[33,34,60] and treatment should be continued through 36 weeks of gestation.[61] Indeed, early discontinuation of therapy appears to increase the risk of recurrent preterm birth.[61] Of note, a history of a prior preterm delivery of twins should not be written off to the multiple gestation alone. Women with such a history are at risk of a recurrent preterm birth even if the subsequent pregnancy is a singleton,[62] and should be considered as candidates for progesterone supplementation.

ACOG recommends that progesterone supplementation be restricted to women with a singleton pregnancy and a previous history of spontaneous preterm birth.[58] That said, there are other circumstances in which progesterone supplementation should be considered (Table 3). The major secondary indication is cervical shortening.[42,44] Women with a shortened cervix ($\leq$ 1.5 cm) on transvaginal ultrasound in the midtrimester should be considered for progesterone supplementation. Because both clinical trials used vaginal progesterone,[42,44] it would be reasonable to recommend this route of administration.

Although supplemental progesterone does appear to be effective in preventing preterm birth in some high-risk women, *it should not be seen as a panacea*. At best, progesterone supplementation prevents only one-third of recurrent preterm births,[33,34] and the long-term benefits of progesterone supplementation are not yet clear. An analysis of 2002 national birth certificate data demonstrated that, even if all eligible women had received progesterone prophylaxis, it would only have reduced the overall preterm birth rate in the United States by approximately 2% (from 12.1% to 11.8%).[63] This is because only 22.5% of preterm births in 2002 were recurrent and prophylaxis only reduces the incidence of recurrent preterm birth by approximately 33%.

Proposed Mechanisms of Progesterone Action

Since the resurgence of interest in progesterone supplementation in 2003, an environment of healthy skepticism and vigorous debate has existed. This debate has been fueled by the facts that (i) not all studies have shown a benefit[35]; (ii) progesterone supplementation does not work in multiple pregnancies[30,51,53-56]; (iii) at best, progesterone supplementation only prevents recurrent preterm birth in one-third of cases[33,34]; and (iv) there are concerns about biologic plausibility. Questions about the mechanism of action of progesterone have focused on the observations that progesterone supplementation does not appear to significantly alter circulating steroid levels[34,64] and that basal levels of 17P in the maternal circulation far exceed that of the dissociation constant for the progesterone receptor. How then does progesterone act to prevent preterm labor and delivery?

Although levels of progesterone in the maternal circulation during labor are not different from that measured 1 week prior,[65] there is increasing evidence to suggest that labor, both at term and preterm, is preceded by a functional withdrawal of progesterone action at the level of the uterus.[27,66-68] A number of mechanisms have been proposed to explain how progesterone may act to maintain uterine quiescence and prevent preterm birth:

- **At the Level of the Myometrium and Cervix:** Progesterone has numerous effects on the myometrium and cervix. It differentially regulates the expression of the two major isoforms of the progesterone receptor (PR) gene, PR-A and PR-B, leading at term to a PR-A/PR-B ratio that favors myometrial contractility and cervical effacement.[25,69] It alters the expression of PR coactivators and histone acetylation within myometrial cells, which are key regulators of myometrial contractility.[24] It interferes with oxytocin binding and signaling in a nongenomic fashion by binding directly with the transmembrane oxytocin receptor.[70] It alters immune function both systemically and at the maternal-fetal interface.[64,71] And most recently, it has been shown to modulate myometrial expression of a number of miRNA-200 family members and their targets, ZEB1 and ZEB2, which, in turn, directly regulate the expression of key contraction-associated genes, including the oxytocin receptor and connexin-43.[26]
- **At the Level of the Placenta:** Progesterone has been shown to interfere with cortisol-mediated regulation of placental gene expression, the most important of which is placental corticotropin-releasing hormone (CRH),[72,73] which has been implicated as the "placental clock" regulating the timing of labor.
- **In Amniotic Fluid:** Progesterone has been shown to upregulate an endogenous inhibitor of phospholipase A_2,[74] which is present in high concentrations in amniotic fluid. High levels of such an inhibitor would serve to limit the availability of arachidonic acid and thereby the production of prostaglandins.
- **At the Level of the Fetal Membranes:** One third of preterm birth occurs in the setting of PPROM. Recent studies have shown that progesterone is able to inhibit apoptosis (programmed cell death) in term fetal membranes both under basal conditions and in the setting of inflammation.[75] These data suggest that progesterone may block proinflammatory cytokine-induced apoptosis within the fetal membrane,

thereby preventing PPROM and subsequent preterm birth.

Taken together, these factors explain how it is possible for progesterone supplementation to maintain uterine quiescence and prevent preterm birth without altering circulating progesterone levels by acting directly at the level of the uterus and cervix to circumvent the functional withdrawal seen in these tissues.

Dispelling the Myths of Progesterone Supplementation

Several areas of controversy still exist regarding the use of progesterone supplementation to prevent preterm birth. These are discussed below.

(1) Selecting the Appropriate Formulation and Route of Administration. The optimal progesterone formulation, route of delivery, and dose for the prevention of preterm birth has not yet been determined.[58,76] There is evidence from in vitro and animal research that the type of progestin, formulation, dose, and route of delivery may have a significant impact on efficacy.[36,37] These factors likely played a role in the discordant findings reported in the clinical trials discussed above. Not all progesterone is created equal. Two major types of progesterone are described:

- **Synthetic Progestins:** These include such agents as medroxyprogesterone acetate and norethindrone acetate. They are typically given by injection, and may have significant androgenic activity.
- **Natural Progesterone:** These agents include progesterone powders, capsules, and gels as well as injectable progesterone-in-oil. They can be given vaginally, orally, or by injection. The advantage of vaginal progesterone is its high uterine bioavailability because uterine exposure occurs before the first pass through the liver. It also has fewer systemic side effects, although vaginal irritation can be bothersome. Because vaginal progesterone has a half-life of approximately 13 hours,[77] it should be administered daily. Doses of 90 to 400 mg have been recommended. An oral micronized preparation of natural progesterone also exists, although daily doses of 900 to 1600 mg have to be given. Side effects include sleepiness, fatigue, and headache.[35,78] The only study to date to investigate the effect of oral micronized progesterone (400 mg daily) on the rate of recurrent preterm birth was underpowered to detect any significant difference, with a total of only 33 study subjects.[79] 17P is a natural progesterone with no androgenic activity that is produced by both the corpus luteum and placenta. Exogenous 17P is administered intramuscularly. Doses have ranged from 25 mg every 5 days to 1000 mg weekly, beginning as early as 16 weeks of gestation. Because the half-life of 17P is approximately 7 days,[80] weekly dosing would seem most appropriate. Although actively metabolized in the placenta, significant concentrations of exogenous 17P and its metabolites do cross the placenta.[81]

(2) Safety of Progesterone Use in Pregnancy. The safety of 17P in pregnancy has been confirmed by numerous epidemiologic studies[82–84] and clinical trials.[33–35] This point was repeated again in the recent FDA statement approving 17P for use in pregnancy.[1] Several studies have suggested that the risk of miscarriage and stillbirth may be increased in women exposed to progestins,[34,48,51,53] but none of these differences reached statistical significance. Moreover, not all studies were able to confirm this observation,[54] and yet others have suggested that progestins may be protective in this regard.[55,85] Although they did not think that this issue should hold up approval or implementation, an Advisory Committee to the FDA suggested that this association should be studied further.[86] The only concern that persists is a possible increased risk of hypospadias in male offspring exposed to exogenous progestins[87,88]; even if real, however, this risk is limited to exposure prior to 11 weeks of gestation and, as such, is not relevant to the current discussion.

Economic Analyses of Progesterone Supplementation

In light of the discussion above, the potential clinical benefits of progesterone supplementation appear large, whereas the risks seem small in comparison. A number of investigators have carried out formal economic analyses in an attempt to quantify the benefit. These include: (i) cost-effectiveness analysis, which is designed to evaluate whether the cost of a given intervention is worth the clinical improvement that it generates, (ii) cost-utility analysis, a type of cost-effectiveness analysis in which the results are reported in quality-adjusted life years (QALY); a threshold of $50,000 to $100,000 per QALY is generally used to determine whether an intervention is cost effective; and (iii) cost-benefit analysis, which considers all of the outcomes in a more complex economic analysis. An intervention is deemed cost beneficial if it leads to overall financial savings. Thus, whereas the cost-benefit analysis of a given intervention is only

positive if it saves money, a cost-effectiveness analysis is designed to determine whether the costs are worth the outcomes achieved.

There have been several economic analyses of the use of 17P for the prevention of recurrent preterm birth. In the cost-utility analysis by Odibo and colleagues,[89] the authors report that the use of 17P is associated with both a reduction in cost and an improvement in perinatal outcome. Such a finding is called a *dominant strategy*. This was true when modeling for women with a prior preterm birth < 32 weeks of gestation and for women with a prior preterm birth at 32 to 37 weeks of gestation. In their cost-benefit analysis, Bailit and Votruba[90] estimated the societal benefits of treating all women with a prior preterm birth with 17P at approximately $1.98 billion. However, if progesterone could prevent preterm birth in women at risk during their first pregnancy, the savings might be even larger. In a recent cost-utility analysis, Cahill and colleagues[91] found that a protocol of screening all women for cervical length and administering vaginal progesterone to those with cervical shortening was both a cost-effective and dominant strategy. An independent cost-effectiveness analysis by Werner and colleagues[92] reached the same conclusions. This analysis suggested that, for every 100,000 women screened and treated, approximately $12,120,000 could be saved, 424 QALY could be gained, and 22 cases of neonatal death or long-term neurologic deficits could be prevented. All of these analyses estimated the cost of 17P supplementation during pregnancy at between $200 and $440.[89-92] If the price of 17P were to change, the use of 17P supplementation would still be cost effective, although the absolute cost saving to society would likely change.

Conclusions

Preterm birth complicates one in eight deliveries and remains a major cause of perinatal morbidity and mortality. Strategies to prevent preterm birth have to date been largely unsuccessful. On February 3, 2011, the FDA approved the use of progesterone supplementation to prevent recurrent preterm birth. Although questions about the optimal formulation, dose, and route of administration remain, this approval coupled with supportive statements by the ACOG and the absence of proven alternatives means that *the use of progesterone supplementation to reduce the risk of recurrent preterm birth in women with a history of a prior preterm delivery can no longer be regarded as investigational.*

Main Points

- In 2008, the latest year for which data are currently available, the overall preterm birth rate in the United States was 12.3%. This represents a 35% increase in overall preterm births over the past 25 years, and has been accompanied by an increase in moderately preterm (28-34 weeks) and extreme preterm births (< 28 weeks).
- Preterm birth represents a syndrome rather than a diagnosis because the etiologies are varied. Approximately 20% of preterm deliveries are iatrogenic and are performed for maternal or fetal indications, including, among others, preeclampsia, placenta previa, prior high-vertical ("classical") cesarean delivery, monochorionic-monoamniotic twins, cholestasis, intrauterine growth restriction, and nonreassuring fetal testing. Of the remaining cases, approximately 20% to 30% occur in the setting of preterm premature rupture of the membranes (PPROM), 20% to 25% result from intra-amniotic infection and/or inflammation, and the remaining 25% to 30% are due to spontaneous (unexplained) preterm labor.
- Predictive tests include risk factor scoring, sonographic cervical length measurement, and biochemical tests.
- It is now clear that, although levels of progesterone in the maternal circulation do not change significantly in the weeks preceding labor, the onset of labor both at term and preterm is associated with a functional withdrawal of progesterone activity at the level of the uterus. It is data such as these that provide the rationale behind the use of progesterone supplementation to prevent preterm labor and birth.
- Although secondary analyses of clinical trials have suggested that women who benefit most from 17P supplementation are those who experienced a prior spontaneous preterm birth < 34 weeks, it is reasonable to offer such prophylaxis to all women with a prior spontaneous preterm delivery.
- Although supplemental progesterone does appear to be effective in preventing preterm birth in some high-risk women, *it should not be seen as a panacea*. At best, progesterone supplementation prevents only one-third of recurrent preterm births, and the long-term benefits of progesterone supplementation are not yet clear.
- The potential clinical benefits of progesterone supplementation appear large, whereas the risks seem small in comparison.

Appropriate candidates should be counseled about the potential benefits of progesterone supplementation from 16 to 20 weeks through 36 weeks of gestation to prevent preterm birth in any subsequent pregnancy. There is evidence that women with cervical shortening (≤ 1.5 cm) on transvaginal ultrasound may also benefit, although this indication has not yet been approved by the FDA. Women with multiple pregnancies do not appear to benefit. Even in ideal candidates, progesterone supplementation has been shown to prevent recurrent preterm birth in only one-third of subjects. A better understanding of the molecular mechanisms by which progesterone acts to maintain myometrial quiescence and prevent uterine contractions and cervical change will allow obstetric care providers to develop interventions that may be more effective and generalizable in years to come. ■

The authors report no real or apparent conflicts of interest.

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